- 34 -

CLAIMS:

1.   A method of determining a sequence to administer multiple types of chemotherapeutic drugs for killing cancerous cells to reduce the induction of drug cross-resistance in a patient, comprising the steps of:

(a)   providing an isogenic panel of cell lines derived from the same tumor type as said cancerous cells, said panel comprising a parental strain sensitive to all of said drugs and two or more progeny strains each being resistant to a separate of said chemotherapeutic drugs;

(b)   assessing the sensitivity of each of said progeny strains to each of said drugs relative to the drug-sensitive parental strain to thereby determine the resistance and cross-resistance of each of said strains to each of said drugs;

(c)   determining an order of administering said drugs using the said sensitivity information, wherein the drug which corresponds to the strain which demonstrates the least resistance to the others of said drugs is determined to be the first to be administered while any other drug which corresponds to a strain which demonstrates a greater cross-resistance is assigned a value as a subsequent drug to be administered.

2.   A method as defined in claim 1 wherein said drugs are assigned ascending values for the order of administration from the drug which corresponds to the strain which demonstrates the least cross-resistance to said drugs to the drug corresponding to the strain which demonstrates the most cross-resistance.

3.   A method as defined in claim 2 wherein said values are determined by assigning a resistance factor to each of said strain/drug combination comprising the ratio of the amount of a selected drug required to kill 50% of said cells of said strain divided by the amount of said selected drug required to kill 50% of the cells of said parent strain, and generating an X by Y cross resistance array wherein one axis represents said strains and the other axis represents each of said drugs, with the resistance factors being entered

within said array for each intersection between X and Y entries, and using said array to assign said ascending values.

4. The method defined in claim 1 wherein said cancerous cells are selected from breast and uterine cancer cells.

5. The method defined in claim 1 wherein said drugs are selected from paclitaxel, doxorubicin, epirubicin, 5-fluoroacil, irinotecan, vinblastine, methotrexate, cisplatine, valspodar, cyclophosphamide, mitoxantrone, topotecan, and bisantrene.

6. Use of caspase-9 or procaspase-9 to prepare a medicament to enhance the effectiveness of an anthracycline anticancer drug in a patient resistant to treatment by said anthracycline.

7. A method of determining resistance of cancerous cells to killing by an anthracycline drug, comprising the step of determining the expression of caspase-9 or procaspase-9 within said cells and identifying said resistance upon determining reduced production of caspase-9 or procaspase-9 within said cells.

8. A method of screening drug candidates to select a lead anticancer drug from amongst a plurality of candidate drugs, said lead having a reduced capacity to induce cross resistance in a patient against one or more known anticancer drugs, all of said drugs having the ability to kill cancerous cells of the same selected tumor type, said method comprising the steps of: providing a panel of isogenic cell lines derived from the same tumor type as said cancerous cells, said panel comprising a parental strain sensitive to all of said drugs and one or more progeny strains each being resistant to a separate of said anticancer drugs; assessing the sensitivity of each of said progeny strains to each of said drugs relative to the drug-sensitive parental strain to thereby determine the resistance and cross-resistance of each of said drugs; and thereby determining as said lead drug the drug which

corresponds to the strain which demonstrates the least resistance to said one or more known drugs.

9.   A method as defined in claim 8 wherein said drug candidates comprise a plurality of related candidate drugs.

10.   A method as defined in claim 9, wherein said drug candidates comprise a plurality of forms of a single candidate drug, said forms being selected from one or more of structural isomers, positional isomers, polymorphic (crystalline or amorphic) forms, chemical analogs, salts, and tautomers.

11.   A method as defined in claim 8 wherein said tumor type is selected from one of breast and uterine tumors.

12.   A panel comprising a plurality of isogenic cell lines all derived from a single cancerous tumor, each said line comprising a population of isogenic cells, a first said population comprising a parental strain sensitive to a plurality of selected chemotherapeutic drugs, and at least second and third of said populations each being resistant to a different one of said drugs, each of said populations being isogenic with the others of said populations.

13.   A panel as defined in claim 12, wherein said cancerous tumor is selected from breast and uterine tumors.

14.   A panel as defined in claim 13, wherein said drugs are selected from paclitaxel, doxorubicin, epirubicin, 5-fluoroacil, irinotecan, vinblastine, methotrexate, cisplatine, valspodar, cyclophosphamide, mitoxantrone, topotecan, and bisantrene.

15.   A method of determining a sequence to administer multiple types of cytotoxic drugs for killing undesired cells to reduce the induction of drug cross-resistance in said cells, comprising the steps of:

(a)   providing an isogenic panel of cell lines derived from the same cell type as said undesired cells, said panel comprising a parental strain sensitive to all of said drugs and two or more progeny strains each being resistant to a separate of said drugs;

(b)   assessing the sensitivity of each of said progeny strains to each of said drugs relative to the drug-sensitive parental strain to thereby determine the resistance and cross-resistance of each of said strains to each of said drugs;

(c)   determining an order of administering said drugs using the said sensitivity information, wherein the drug which corresponds to the strain which demonstrates the least resistance to the others of said drugs is determined to be the first to be administered while any other drug which corresponds to a strain which demonstrates a greater cross-resistance is assigned a value as a subsequent drug to be administered.

16.   A method as defined in claim 15 wherein said drugs are assigned ascending values for the order of administration from the drug which corresponds to the strain which demonstrates the least cross-resistance to said drugs to the drug corresponding to the strain which demonstrates the most cross-resistance.

17.   A method as defined in claim 16 wherein said values are determined by assigning a resistance factor to each of said strain/drug combination comprising the ratio of the amount of a selected drug required to kill 50% of said cells of said strain divided by the amount of said selected drug required to kill 50% of the cells of said parent strain, and generating an X by Y cross resistance array wherein one axis represents said strains and the other axis represents each of said drugs, with the resistance factors being entered within said array for each intersection between X and Y entries, and using said array to assign said ascending values.

18. A complete panel of isogenic drug-resistant MCF-7 breast tumor cell lines deposited at The International Depositary Authority of Canada (IDAC) under the accession numbers 271104-01 and 271104-02.